CHAPTER 9: BONE HEALTH AND THE EXERCISING FEMALE

Jacky Forsyth **ORCID ID: 0000-0002-9646-9246**

Karen Hind **ORCID ID: 0000-0002-4546-5536**

Abstract

Optimising bone health throughout the lifespan is vital for the prevention of osteoporosis and fracture. Exercise is one of the most important, modifiable determinants of bone strength, although high levels of exercise, particularly if coupled with energy deficiency and menstrual dysfunction, can lead to bone decrements in the exercising female. In this chapter, an overview of bone physiology is given, with a focus on how bone responds to loading through exercise, and to hormone and endocrine activity. The current evidence is reviewed and recommendations provided.

Introduction

The benefits of regular exercise throughout the lifespan are well recognised, with certain types of exercise more beneficial to bone than others. In contrast, high levels of endurance exercise, and participation in sports that emphasise leanness, have been associated with low bone strength, bone loss and elevated stress fracture risk. In females, these skeletal problems are mainly reported in athletes displaying Female Athlete Triad conditions, arising from relative energy deficit and/or functional hypothalamic amenorrhoea.

In this chapter, the two main themes of the book are addressed: Low bone density for age and fracture are issues that the exercising female may encounter, often because of relative energy deficit (purposeful or inadvertent), menstrual dysfunction, and endogenous and exogenous changes in oestrogen that occur across the lifespan (Theme 1). How to optimise bone health for the exercising female, to ensure athletic success and longevity of an athletic career, addresses the second theme of the book.

The aims of the chapter are:

- To examine the physiological processes involved in bone remodelling, and the effect of oestrogen and energy deficiency on bone turnover.
- To evaluate the research on the interplay between endocrinology, exercise and bone health.
- To examine strategies to support bone health for the exercising female and how to effectively maximise bone strength.

Osteoporosis

Osteoporosis is characterised by low bone mineral density (BMD) and architectural deterioration of bone. For women, bone loss and osteoporosis are of particularly concern, since around 50% of females suffer an osteoporotic fracture in their lifetime (Randell et al., 1995). Common sites of fragility fracture are the femoral neck, distal radius, and vertebrae. Fractures can lead to a loss of independence, a reduction in quality of life and an increase in premature mortality. Osteoporosis is known as a 'silent disease' in that bone loss is not realised until fracture. Thereafter, secondary prevention is key. Nonetheless, the most tangible approach to reducing fracture risk is through primary prevention. The maximisation of bone mass during adolescence, maintaining optimal bone mass during the premenopausal years, and reducing the rate of postmenopausal bone loss are critical for avoiding osteoporotic bone fracture.

The measurement of bone

The most widely used and universally recognised method for bone health assessment is dual energy X-ray absorptiometry (DXA). This method provides a highly precise measurement of BMD (Carey & Delaney, 2017; Hind, Oldroyd, & Truscott, 2010), and uses low iodising radiation with bone density evaluations typically equivalent, or less, than two days of natural background radiation. A bone density assessment by DXA usually includes scans of both the lumbar spine and total hip, with each scan only taking several minutes. Areal BMD (g/cm^2) measured by DXA is a robust

predictor of fracture risk (Cummings et al., 1993). The Z- and T-score scales measure the deviation from age- and sex-matched and young normal mean values, respectively, and are calibrated in SD units. A 1-SD decline in BMD results in around a doubling of fracture risk (Marshall, Johnell, & Wedel, 1996).

In postmenopausal females, osteoporosis is defined as a BMD T-score that is -2.5 or less, and osteopaenia as a BMD T-score that is between -1.0 and -2.4 (Kanis & Kanis, 1994). In people aged under 50 years, low BMD is identified as a Z-score that is equal to or less than -2.0, although -1.0 also indicates suboptimum BMD, particularly for exercising females who require stronger bones for repetitive or higher impact activities. The definitions of osteoporosis and low BMD for age, are further described in the official Positions of the International Society of Clinical Densitometry (Schousboe, Shepherd, Bilezikian, & Baim, 2013).

Volumetric BMD is assessed using medical imaging such as peripheral quantitative computed tomography (pQCT). This method can clearly distinguish between the different types of bone tissue, and high resolution pQCT systems provide advanced information on the bone microarchitecture, which is an independent risk factor for fracture. Over the last decade, studies of bone architecture in female athletes from various sports demonstrate the osteogenic effects of loading (e.g., Kontulainen, Sievänen, Kannus, Pasanen, & Vuori, 2003; Nikander, Sievänen, Uusi-Rasi, Heinonen, & Kannus, 2006). Athletes with amenorrhoea demonstrate lower cortical volumetric BMD (Ackerman et al., 2011), which suggests an increased risk of fracture as a result of menstrual disturbances.

Bone structure and bone turnover

There are two types of bone tissue–cortical and trabecular, which differ according to structure, function and location. In cortical bone, the structural unit is the Haversian system or osteon, which runs the length of the bone, and consists of concentric layers or lamellae. Cortical bone has a high resistance to torque, and has a slow bone turnover rate. It is found on the outer surfaces of most bones and in the shafts of long bones.

Trabecular bone consists of a matrix, called trabeculae. This mesh-like design enables trabecular bone to withstand sudden stresses that occur through the joints during loading. Bone remodelling takes place predominantly within trabecular bone, and it is where haematopoiesis and mineral (calcium and phosphate) metabolism takes place. Trabecular bone is more associated with osteoporosis, and more sensitive to oestrogen deficiency (Beerthuizen et al., 2000). It is found mainly at the ends of long bones, and in the internal portions of other bones, such as the spine and pelvis. Approximately 80% of the skeleton consists of cortical bone, and 20% of trabecular bone (Eriksen, Axelrod, & Melsen, 1994).

There are five main types of bone cell: bone-lining cells, osteoprogenitor cells, osteoblasts, osteocytes, osteoclasts. Bone-lining cells remain on the bone surface when there is no active bone growth. Osteoprogenitor cells are derived from mesenchymal stem cells, and differentiate into osteoblasts, the bone-forming cells,

found at the bone surface. Osteocytes are the mature bone cells, found deep within the bone matrix in small lacunae (spaces), and are also central to mechanotransduction (sensing and responding to mechanical loading). Osteoclasts, derived from osteoclastic precursors, develop and differentiate to become mature, bone-resorbing cells.

Throughout life, bone is in a constant state of remodelling through bone resorption (removal) and bone formation. Bone remodelling occurs in response to the need for calcium in the extracellular fluid, to mechanical stress on the bone (e.g., through exercise), and to changes in hormones. Following bone resorption, osteoblasts migrate to the resorption pit, and secrete collagen and various proteins, creating osteoid, which is uncalcified bone tissue. Osteoblasts assist with the calcification of the osteoid, involving the secretion of alkaline phosphatase, osteocalcin and osteonectin (Florencio-Silva et al., 2015). The whole remodelling cycle takes approximately three months.

Endocrine and hormone effects

Bone turnover is modulated by a wide variety of hormones/endocrine activity. Of primary importance for women's bone health is the hormone oestrogen, which comprises a group of steroid hormones (oestradiol, oestriol and oestrone), produced by the ovaries in women and in small amounts by the male testes and adrenal cortex. Oestrogen has a necessary role in the development and maintenance of BMD. Deficiencies, such as that arising from the menopause, can bring rapid bone loss. Oestrogen deficiency can also occur in young women, who exercise excessively

and/or eat too little; secondary hypothalamic amenorrhoea (present when a female, with previously normal menstrual cycles, has fewer than three menstrual cycles per year) is an acquired gonadal-releasing hormone deficiency, leading to ovarian suppression and a deficiency of the sex steroids.

The interaction of oestrogen within the bone remodelling process involves tumour necrosis factor (TNF) cells: RANKL (the name is derived from Receptor Activator of Necrosis factor-Kappa B Ligand), RANK and osteoprotegerin (OPG) (Rosen, 2013; Scheurer, 2013). RANKL is expressed by osteoblasts, and plays a key role in bone resorption, through its binding with its receptor, RANK, which is expressed on the surface of osteoclast precursors. This binding activates signalling pathways that promote fusion, differentiation, and maturation of osteoclasts. Osteoblasts also express OPG, which works as a decoy receptor for RANKL, by preventing the binding of RANKL to RANK.

With optimal oestrogen levels, RANKL expression by osteoblasts is inhibited, and OPG blocks the binding of RANKL to RANK; osteoclastic activity is reduced. Suboptimal levels of oestrogen (leading to an increase in pro-inflammatory cytokines, such as interleukin-1 [IL-1]) result in an increased expression of RANKL (Schett, 2011). Osteoprotegerin, which also decreases, is unable to block the binding of RANKL to RANK, being overwhelmed by the excessive expression of RANKL. Increased osteoclastic activity results and outstrips the pace of osteoblastic activity, leading to net bone loss (Marques et al., 2013; Xiong & O'Brien, 2012). Oestrogen

also exerts its influence on bone formation through an increase in pro-inflammatory cytokines (Manolagas, 2013).

There are several other hormones, relevant to women, that can influence bone metabolism. Increases in follicle-stimulating hormone (FSH) (for example during the perimenopause, prior to a notable reduction in oestrogen, or in subclinical menstrual dysfunction) can impact bone metabolism through osteoclast FSH receptors and FSH increased expression of RANKL (Colaianni, Cuscito, & Colucci, 2013). Reductions in testosterone promote osteoclastogenesis and decrease bone formation and calcium absorption (Chen, Kaji, Kanatani, Sugimoto, & Chihara, 2004). In women, as in men, androgens also have independent effects on bone development (Manolagas, O'Brien, & Almeida, 2013).

Exercise and bone health

Bone adapts to its habitual loading environment and responds to a wide range of biochemical and physical stimuli. In particular, the musculoskeletal loading sustained during exercise is a major osteogenic stimulus. Exercise has an undisputed role for the attainment of peak bone mass, and the subsequent maintenance of bone as a prophylaxis against osteoporosis. The mechanism by which bone adapts to loading is well described in the mechanostat theory (Frost, 1987), which proposes that survival of the skeleton depends on the functional coordination of bone modelling and remodelling, and that when all else is equal, individuals who are physically active will possess stronger bones than their less active peers. Evidencing the mechanostat,

superior bone strength is frequently reported in female athletes from sports such as gymnastics, running and alpine skiing compared to nonathletic peers or athletes from non-weightbearing sports (Hind, Gannon, Whatley, Cooke, & Truscott, 2012; Sievänen et al., 2015), as well as positive skeletal effects from impact- or resistance-exercise (Tucker, Strong, LeCheminant, & Bailey, 2015; Watson et al., 2018).

Cellular responses to loading

At the molecular level, osteocytes sense bone loading through impacts (gravitational) or directly from muscle forces upon bone. Osteocyte mechanosensation is facilitated through plasma membrane disruption (Yu et al., 2017). When bone is loaded, movement of interstitial fluid creates shear stress on the cell membrane of the osteocytes instigating mechanotransduction processes (Robling & Turner, 2009). Osteocytes respond through calcium signalling to osteoblasts and osteoclasts (Marques et al., 2013), which leads to a decrease in RANKL/OPG ratio (Robling & Turner, 2009). Loading of bone also downregulates sclerostin expression via osteocytes (Xiong & O'Brien, 2012), which increases bone formation via relieving inhibition of canonical Wnt signalling in osteoblasts and through regulating OPG, which suppresses the resorptive activity of osteoclasts (Galea, Lanyon, & Price, 2017).

Optimal exercise for bone health

Animal studies have provided important insights for our understanding of the key components of an optimal exercise programme. It has been clearly demonstrated that dynamic rather than static loads, high strain magnitudes, high strain rates, rapid strain

reversal, and unusual frequency distributions provide optimal osteogenic stimuli (Ehrlich & Lanyon, 2002; Rubin, Sommerfeldt, Judex, & Qin, 2001). The duration of load and the number of loading cycles appear to be of minor importance, whereas rest periods between bouts of loading have a positive role (Robling, Burr, & Turner, 2000).

In humans, exercise that mimics the loading patterns identified in animal studies have been successful in increasing bone health. For instance, jumping interventions are particularly efficacious for improving femoral BMD, and especially if undertaken as short-discrete bouts (Babatunde & Forsyth, 2013; Babatunde, Forsyth, & Gidlow, 2012; Martyn St-James & Carroll, 2010; Zhao, Zhao, & Zhang, 2014). In contrast, walking and jogging bring about relatively modest improvements in bone health (Martyn-St James & Carroll, 2008; Palombaro, 2005), likely reflecting the habituation and desensitisation to the continuous loading and repetitive nature of these activities. Athletes involved in non-weightbearing sports, such as cyclists, can have lower BMD than athletes participating in weightbearing sports, to a level that is similar to or less than their nonactive peers (Campion et al., 2010; Hind et al., 2012). It is also important to consider that the skeletal response to loading is localised to the focus of strain, which means that any changes in bone mass and structure are site specific. This localisation is clearly demonstrated through greater bone strength in the dominant versus nondominant forearms of racquet sports' players (Ducher, Tournaire, Meddahi-Pellé, Benhamou, & Courteix, 2006; Kontulainen et al., 2003), in the upper body of gymnasts (Burt, Greene, Ducher, & Naughton, 2013), and in the greater BMD of the lower limbs compared to the spine in long-distance runners (Hind, Truscott, & Evans, 2006).

As well as gravitational loading, skeletal muscles provide an osteogenic driving force. Resistance training programmes can be designed to develop muscle and bone strength throughout the whole body and resistance can be adjusted to suit the level of the individual. Regular strength training is associated with higher BMD in female distance runners regardless of amenorrhoea (Hind et al., 2006), and in intervention studies, improved BMD in premenopausal women and prematurely menopausal women have been reported following resistance training interventions (Watson et al., 2018; Winters-Stone et al., 2013). From the evidence to date, exercise programmes should include not only gravitational, impact loading to the skeleton, but also exercises that develop muscle strength.

The Female Athlete Triad and bone health

The Female Athlete Triad is characterised by the three inter-related components of low energy availability, altered menstrual function and low BMD. Reduced energy availability or relative energy deficit is the key driver of the Triad and occurs when there is a failure to match calorific energy intake with exercise energy expenditure. Over time, energy deficit can negatively affect bone health in female athletes through a) effects on the hypothalamic pituitary ovarian axis and b) effects on metabolic hormones and substrates. The Triad is covered in more detail in Chapter 8.

Athletes with longstanding functional hypothalamic amenorrhoea have been shown to benefit less from the osteogenic effects of exercise (Ackerman et al., 2012; Bonis,

Loftin, Speaker, & Kontos, 2009). Even subtle alterations in the oestrogen/progesterone imbalance (e.g., regular menstruation but alterations in luteinising hormone), as seen in subclinical ovulatory disturbances, may adversely impact bone, particularly at trabecular-bone-dominant sites, such as the spine (Li, Hitchcock, Barr, Yu, & Prior, 2014). With optimal levels of oestrogen, exercise brings a greater osteogenic response than either exercise alone or oestrogen alone (Balasch, 2003).

Other endocrine disturbances from energy deficit include hypercortisolaemia, growth hormone resistance, reductions in insulin-like growth factor-1 (IGF-1) and suppressed 3,5,3 triiodothyronine ('low T_3 syndrome') (Zanker & Cooke, 2004). Each have been shown to influence bone turnover; for example, hypercortisolaemia limits osteoblastic function and increases osteoclastic activity (Bressot et al., 1979), while reductions in IGF-1 retard the activity of osteoblasts and bone collagen synthesis (Yakar et al., 2002). In studies where an energy deficit has been experimentally induced in exercising females, significant reductions in IGF-1 and triiodothyronine (TT_3), with corresponding reductions in bone formation, have been demonstrated, indicating that low energy availability directly affects bone metabolism (Ihle & Loucks, 2004). Prolonged relative energy deficit also brings disruptions in the body's nitrogen balance (Zanker & Cooke, 2004), which can lead to further negative effects on skeletal integrity through a loss of muscle mass and muscle strength (Kortebein, Ferrando, Lombeida, Wolfe, & Evans, 2007).

In the short term, amenorrhoea and energy deficit in female athletes are associated with an increased risk for skeletal injury such as stress fracture and stress reaction (Barrack et al., 2014). There have been case reports of displaced femoral neck fractures in amenorrhoeic female long-distance runners after continuing to run on untreated femoral neck stress fractures (Goolsby, Barrack, & Nattiv, 2012; Okamoto, Arai, Hara, Tsuzihara, & Kubo, 2010). These athletes also had a history of disordered eating and low body mass. The long-term effects on bone strength are unclear but researchers indicate that, in some cases, bone density is recoverable through weight gains and resumption of menses, at least by the age of 30 years (Hind, 2008; Hind, Zanker, & Truscott, 2011).

Contraceptives and bone health

The effects of contraceptives on bone health and performance in female athletes has been a topic of much interest over the last few decades. Hormone-based contraceptives are used, by some, for the purposes of regulating or manipulating menses and associated symptoms, as well for its intended purpose (see Chapter 4 for a full review). The BMD of combined oral contraceptive (OC) users has been found to be lower than that of non-users (Hartard et al., 2007; Prior et al., 2001), although many researchers have found no change in BMD with OC use (e.g., Hind, Truscott, & Carroll, 2008; Nappi, Bifulco, Tommaselli, Gargano, & Di Carlo, 2012). The mixed findings concerned with OC use might be explained by the ratio of progesterone to oestradiol found in the different OC preparations (Nappi et al., 2012), and the type of concomitant exercise undertaken. The use of OCs might also lower the setpoint for

mechanical adaptation as a result of exercise (Hartard, Bottermann, Bartenstein, Jeschke, & Schwaiger, 1997; Weaver et al., 2001).

Using progesterone-only contraception, in particular Depot Medroxyprogesterone Acetate (DMPA), also known as DepoProvera®, can decrease BMD, especially with sustained use, among adolescents and with advancing age (Curtis & Martins, 2006; Shaarawy, El-Mallah, Seoudi, Hassan, & Mohsen, 2006). The use of DMPA and concurrent engagement in high levels of exercise may not be as beneficial to bone health as exercise undertaken without DMPA use (Babatunde & Forsyth, 2014). In the hypo-oestrogenic state, mechanical strain, brought about through exercise, could downregulate oestrogen receptor (ERα) expression (Zaman, Cheng, Jessop, White, & Lanyon, 2000) and hence impair the osteocytes' signalling capability. It is, therefore, important, to self-regulate hormone-based contraceptive use, and to check bone health and oestrogen status regularly.

The menopause, exercise and bone health

The menopause can negatively impact bone metabolism and lead to net bone loss. In response, there have been numerous studies to explore the effectiveness of exercise for protecting bone health in postmenopausal women. The results have been mixed and are likely to reflect differences in exercise modalities and exercise compliance (Howe et al., 2011; Kelley & Kelley, 2006). In interventions that have included high-impact activity, such as impact loading and jumping, BMD improvements have been modest (Bolton et al., 2012), although others have reported more beneficial osteogenic effects (Borer, Fogleman, Gross, La New, & Dengel, 2007). Positive

effects have also been reported from interventions where high-magnitude joint loading has been achieved through resistance training (Marques, Mota, & Carvalho, 2012; Watson, Weeks, Weis, Horan, & Beck, 2015). Exercise for this population may counteract the negative effects of hypo-oestrogenism, but it needs to be targeted.

Practical recommendations

- Exercising females should ensure that energy needs are well balanced with sufficient energy intake to support normal menstruation and bone health and reduce the risk of injuries including stress fracture.
- The Female Athlete Triad includes negative consequences for bone strength and therefore exercising females, their coaches and support teams, should recognise signs and seek positive interventions.
- Training programmes for the exercising female, regardless of age or menstrual status, should consist of bone-targeted, multi-component exercise, such as muscle-strengthening exercise, and exercise that is dynamic, of high impact, discrete (with rest bouts), and unusual, with all areas of the body targeted.

‘Real-world’ example

A 21-year-old, international-level, female, long-distance runner displayed all three components of the Female Athlete Triad, with significant and prolonged energy deficit. At first presentation, she was running around 88 km/week, her body mass was

44.3 kg and her lumbar spine, total hip and total body BMD Z-scores were -2.2, -0.5 and -0.3, respectively. She suffered a stress fracture of the left sacrum at first presentation and of the 3rd metatarsal two years later. Six years later, following a recovery plan of 20 weeks consisting of cognitive behavioural therapy (CBT), weight gain (10 kg), improved dietary intake and reduced training load (88 to 22 km/week), she regained menstrual function and BMD. Her lumbar spine, hip and total body BMD Z-scores improved to -0.6, 0.1 and -0.1, respectively. Restoration of fertility was indicated by pregnancy, following only 4 months of regular menstruation. This real-world example suggests that bone density and fertility may be recovered in formerly amenorrhoeic and osteopaenic athletes, through diet, weight gain, and return of menstruation.

Summary

Energy balance and adequate levels of oestrogen are important for the exercising female, since both are a key mediators of bone remodelling. Decrements to bone health can also occur through the use of certain contraceptives, such as progesterone-only contraceptives, and through changes in hormones as a result of menopause. Exercise that specifically targets the bone, such as dynamic, high impact, muscle-strengthening, and discrete bouts of exercise are important for the exercising female, especially when oestrogen is suboptimal, or when the usual exercise undertaken is non-weightbearing.

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